526 Rec'd PCT/PTO 18 SEP 2000

FORM PTO-1390 (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 183-109(US)

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/646493

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US99/04412	01 March 1999	17March 1988

TITLE OF INVENTION: TOPICAL ANTISEPTIC COMPOSITIONS AND METHODS

APPLICANT(S) FOR DO/EO/US: Solomon B. Margolin

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau)
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information.

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U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/646493	PCT/US99/04412	183-109(US)

17 [X] The following fees are submitted	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
Neither international preliminary examination fee (37 CFR 1 482) nor international search fee (37 CFR 1 445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**		
International preliminary examination fee (37 CFR 1 482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**		
International preliminary examination fee (37 CFR 1 482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$760.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 96.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1 492(e))	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	18 - 20 =	0	X $18.00	$	
Independent claims	2 - 3 =	0	X $78.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 96.00	
Reduction of 1/2 for filing by small entity, if applicable A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 48.00	
SUBTOTAL =				$ 48.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1 492(f)) +				$	
TOTAL NATIONAL FEE =				$ 48.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 48.00	
				Amount to be: refunded	$
				charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed

c. [XX] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 03-3838 A duplicate copy of this sheet is enclosed

xx Credit Card Payment Form

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

John H. Crozier
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NAME

30,371
REGISTRATION NUMBER

09/646493
PCT/PTO 18 SEP 2000

Description

Topical Antiseptic Compositions and Methods

Technical Field

The present invention relates to antiseptic compositions and, more particularly, to an ointment, cream, or foam containing pirfenidone and/or related compounds, for disinfecting the skin.

Background Art

A large number of various disinfecting preparations are known. When hygienic purposes are concerned, disinfection becomes rather difficult, because it is necessary to reconcile an efficient antiseptic effect with demonstrable harmlessness with respect to the skin. Many such known disinfecting preparations cause adverse reactions when applied to the skin, such as skin irritation, even though the preparations may have satisfactory antiseptic properties.

Accordingly, it is a principal object of the present invention to provide new disinfectant compositions and methods of application which are harmless to the skin, while exerting a marked killing action on microorganisms which develop on or in the outer layers of the dermis.

It is a further object of the invention to provide such a disinfectant composition as an ointment, cream, or foam formed in an aqueous dispersion of one or more substances, the water of the dispersion being dissolved or emulsified therein and carrying suitable fatty solvents and an active ingredient.

It is an additional object of the invention to provide such a disinfectant composition that is self-sanitizing, that is, the composition causes the complete destruction of bacteria and fungi after the composition has been deliberately inoculated with contaminating infectious microbes.

It is another object of the invention to provide such a disinfectant composition that can be utilized as an antimicrobial disinfectant for various inanimate objects.

It is yet a further object of the invention to provide such a disinfectant that is long lasting because of the persistence of the active agent on the surface of the skin.

It is yet a an additional object of the invention to provide such a disinfectant that penetrates into the several outer layer of the dermis.

It is yet another object of the invention to provide such a disinfectant that is harmless with respect to the skin.

Other objects of the present invention, as well as particular features, elements, and advantages thereof, will be elucidated in, or be apparent from, the following description and the accompanying drawing figures.

Disclosure of Invention

The present invention achieves the above objects, among others, by providing, in a preferred embodiment, a method of treating bacteria, fungi, and/or viruses on the surface of, or within, the layers of the dermis of skin, ears, fingernails, toenails, or hoofs of mammalian species, comprising: applying to said surface or layers a pharmaceutical substance including an effective amount of one or more 2-(1H) pyridone compound(s).

Best Mode for Carrying Out the Invention

The present invention relates to medical compositions and methods for the novel antiseptic topical treatment of microbial (bacteria, fungi, viruses) on the surface of, or within, the layers of the dermis of skin, ears, fingernails, toenails, or hoofs of mammalian species, which composition comprises pirfenidone (5-methyl-1-phenyl-2-(1H) pyridone) and/or related compounds in an appropriate formulation of a pharmaceutical topical ointment, cream, lotion, or solution.

Furthermore, the present invention is directed to a non-irritating, emollient, germicidal pharmaceutical composition. This composition affords a method of using the formulations as antiseptics for untoward skin conditions such as a dermal wound, bruise, or microbial infections, as well as for other damaged external body surface tissues, by safely penetrating outer layers of skin and related tissues or structures. In addition, the antimicrobial data indicate the compositions to be self-sanitizing, since the composition can cause marked elimination or complete destruction of bacteria and fungi after the composition has been deliberately inoculated with infectious microbes. The composition also can be utilized as an antimicrobial disinfectant for various inanimate objects. As formulated, the composition is stable for many months at temperatures of 25 degrees Centigrade or less.

The invention provides an ointment, cream, or foam formed in an aqueous dispersion of one or more active substances, the water of the dispersion being dissolved or emulsified therein and carrying suitable fatty solvents and the active ingredient(s), pirfenidone and/or related compounds. The preferred concentration of the active ingredient(s) is from about 5 to about 10 weight percent.

The composition of the present invention provides an effective microbial sanitizer, disinfectant, and barrier in one composition. The antimicrobial effects are very marked as evidenced by the several tests set forth below.

By adding suitable ingredients to the active compound(s), such as glycerine, natural colorants, surfactants, emulsifiers, and oils, it is possible to produce antiseptic products which are presented as antiseptic lotions, antiseptic solutions, lotions, antiseptic ointments, and antiseptic foams. In the case of antiseptic ointments, creams, lotions, and solutions, the cited bactericidal, fungicidal, and virucidal effects are recognizable within minutes. The antiseptic products and their method of manufacture are illustrated below.

The ingredients of the compositions include USP products: white petrolatum, propylene glycol 400, and stearyl alcohol, for example, all appropriately dissolved and emulsified into purified distilled water. In order to illustrate the general dermatological composition of the present invention, a base composition of the following can be prepared:

MODIFIED USP HYDROPHILIC OINTMENT (5.0% PIRFENIDONE)

Ingredient	Percent by Weight
Pirfenidone (USAN) Powder	5.0
Propylene Glycol 400 USP	23.5
Sterile Distilled Water	30.5
Stearyl Alcohol USP	20.5
White Petrolatum USP	20.5
TOTAL:	100.0

MODIFIED USP HYDROPHILIC OINTMENT (10.0% PIRFENIDONE)

Ingredient	Percent by Weight
Pirfenidone (USAN) Powder	10.0
Propylene Glycol 400 USP	14.3
Sterile Distilled Water	41.7

Stearyl Alcohol USP	17.0
White Petrolatum USP	17.0
TOTAL:	100.0

It is important to mix and melt the aqueous components (pirfenidone, propylene glycol 400, and water), heating to about 70 degrees Centigrade independently from the lipophilic phases (stearyl alcohol and white petrolatum) which also must be heated to about 70 degrees Centigrade to facilitate mixing and melting. When each phase has been adequately mixed and melted, they are combined and cooled with rapid stirring, until the mixture congeals into a fluffy, white ointment. The temperature of the ointment when it congeals will be about 40-45 degrees Centigrade. (Failure to adequately mix by vigorous stirring during the chilling step will result in the separation of the two solvent phases, and the emulsifying properties of the formulation will have been lost.)

A critical feature of the compositions of this invention is the chemical stability of the active ingredient(s), pirfenidone and/or related compounds. Crystalline pirfenidone is stable at room temperature (i.e., 25 degrees Centigrade) for more than five years. The formulations described above are stable for two years or longer at 25 degrees Centigrade (room temperature), based upon chemical assays and upon physical characteristics (color, plasticity, active ingredient dispersion and suspension).

The formulations described above have demonstrated their efficacy against the following microorganisms:

Escherichia coli
Staphylococcus aureus
Bacillus subtilis
Pseudomonas aeruginosa
Proteus vulgaris
Trichophyton mentagorphytes

Candida albicans
Aspergillis niger
Influenza virus
Coxsakie virus
Herpes virus
Papilloma virus

TABLE I

PRELIMINARY ANTIMICROBIAL TEST OF PIRFENIDONE

	Pirfenidone Concentrations, wt.%					
	2.0	0.0*	5.0	0.0*	10.0	0.0*
	GROWTH SCORES (0 TO 10)***					
BACTERIA:						
Proteus vulgaris	-**	-	0	10	0	10
Escherichia coli	-	-	0	10	0	10
Pseudomonas aeruginosa	1	10	0	10	0	10
Bacillus subtilis	-	-	0	10	0	10
Staphylococcus aureus	-	-	0	10	0	10
FUNGI:						
Candida albicans	-	-	2	10	0	10
Aspergillus niger	-	-	0	10	0	10
Trychophton mentagrophytes	-	-	2	10	0	10

* Control.

** Not tested.

*** 1=very slight
2=slight
3=slight to moderate
4=moderate
10=total plate growth (maximal growth)

(End of Table I)

METHODS FOR MEASURING ANTIMICROBIAL ACTIVITY IN TOPICAL PREPARATIONS FOR TABLE I:

TESTING DISINFECTING ACTIVITY

A nutritive broth is prepared by dissolving a commercial nutritive substance in 1000 ml. of sterile distilled water. The solution is heated to 100 degrees Centigrade and poured into sterile Petri dishes under sterile conditions. After cooling and solidifying, the gels are then kept at 37 degrees Centigrade for the specified number of hours or days.

Using the modified USP hydrophilic ointment with and without pirfenidone, the procedure outlined below was followed to determine bacterial and fungal counts. This procedure is based on that described in the booklet "microbiological Examination of Topical Drugs and Cosmetics," published by the Division of Microbiology, United States Food and Drug Administration, January 7, 1969.

Bacteria Plate Count:

Ten (10) grams of sample is aseptically measured into 90 ml. diluent (Butterfield's phosphate diluent with azolectin and Tween 80) to make a 10 (1 pwr) dilution. Decimal dilutions from 10 (1 pwr) to 10 (4 pwr) are made using 90 ml. dilution blanks of Butterfield's phosphate diluent. Duplicate plates from each of the above dilutions are made following directions of AOAC, 11th ed., 1970, pp 842-843, 41.015, except for the use of Trypticase Soy Agar (42-45 degrees Centigrade) in place of plate count agar.

One ml. of each dilution is placed into a Petri dish and Trypticase Soy Agar is added within 15 minutes from the time of original dilution. Plates were incubated for 48 hours at 35 degrees Centigrade, and duplicate plates for each dilution with colony counts in the range of 30 to 300 per plate are counted and

averaged. Counts are reported as aerobic plate count per gram of sample.

Fungi Plate Count:

Decimal dilutions as described above for the aerobic bacteria plate count are prepared. Aliquots of 1.0 ml. of each dilution are delivered to each of quadruplicate (4) plates. Plates are poured with 20-25 ml. of "Sabouraud's Dextrose Agar. Two plates are incubated at 37 degrees Centigrade, and other two plates are incubated at room temperature (26 degrees Centigrade) for seven days. Counts of duplicate plates are averaged and reported, in each case, as counts per gram of sample.

TABLE II

ADDITIONAL PIRFENIDONE ANTI-MICROBIAL PILOT TESTS

Test # 1:.

A 2.0% solution of pirfenidone was prepared in nutrient broth, and then was inoculated with Pseudomonas aeruginosa. After 48 hours of incubation at 37 degrees Centigrade, the nutrient broth failed to evidence any growth. Then a standard loopful from this pirfenidone treated broth was streaked on Tryptic Soy Agar (Difco) and incubated for 5 days at 37 degrees Centigrade; no growth of Pseudomonas aeruginosa was seen.

Test # 2:

A 5.0% solution of pirfenidone in Tryptic Soy Agar (Difco) was formulated. Pirfenidone was dissolved in hot agar. When permitted to cool to room temperature (26 degrees Centigrade), pirfenidone became a suspension in a uniform slightly opaque manner throughout the agar. At 10.0% of pirfenidone in Tryptic Soy Agar, the drug formed a uniformly opaque suspension in the agar. Growth was completely inhibited at both concentrations of the following organisms:

Antiseptic Effect Against Bacteria:

Agar inoculated with the following bacteria, and incubated at 37 degrees Centigrade:

Escherichia coli	ATCC	#11229
Proteus vulgaris	ATCC	# 6538
Bacillus subtilis	ATCC	#19659
Staphylococcus aureus	ATCC	#13315
Pseudomonas aeruginosa	ATCC	#15442

Antiseptic Effect Against Fungi:

Agar inoculated with the following fungi and incubated at 26 degrees Centigrade:

Trichophyton mentagrophytes	ATCC	# 9129
Candida albicans	ATCC	#10259
Aspergillis niger	ATCC	# 9642

(End of Table II)

TABLE III

CHALLENGE TESTS

Challenge tests were conducted of pirfenidone against microbial inoculations into: (a) nutrient broth, and (b) 5.0% or 10.0% pirfenidone ointments (modified USP hydrophilic ointment). A Pseudomonas aeruginosa inoculation into broth served as a positive control.

The bacterial mixture for inoculation consisted of:

Escherichia coli
Proteus vulgaris
Bacillus subtilis
Staphylococcus aureus
Pseudomonas aeruginosa

The fungal mixture for inoculating consisted of:

Trichophyton mentagrophytes
Candida albicans
Aspergillis niger

After seven days, the respective cultures were plated out to determine the number of microbes present. The results as compared with the baseline number of microbes present when the cultures were inoculated follows:

	Pseudomonas (Positive Control)	Mixed Bacteria	Mixed Fungi
	Microbes per gm. of Sample (After 7 days)		
Baseline (day 1) (No Pirfenidone)	52 million (100.0%)	23 million (100.0%)	240,000 (100.0%)
2.0% Broth Solution (Pirfenidone)	<100 (0.0%)	530,000 (2.3%)	2,000 (0.08%)
5.0% Ointment (Pirfenidone)	510,000 0.01%)	57,000 (0.02%)	350 (0.002%)
10.0% Ointment (Pirfenidone)	2,600 (0.0001%)	70,000 (0.03%)	<10 (0.0%)

(End of Table III)

TABLE IV

CHALLENGE EXPERIMENTS

Challenge experiments were conducted over four weeks for pirfenidone ointment against mixed microbial inoculations into: (a) nutrient broth, and (b) 5.0% or 10.0% pirfenidone ointments. A Pseudomonas aeruginosa inoculation into broth served as a positive control.

The bacterial mixture for inoculation consisted of:

Escherichia coli	ATCC	#11229
Proteus vulgaris	ATCC	# 6538
Bacillus subtilis	ATCC	#19659
Staphylococcus aureus	ATCC	#13315
Pseudomonas aeruginosa	ATCC	#15442

The fungal mixture for inoculation consisted of:

Trichophyton mentagrophytes	ATCC	# 9129
Candida albicans	ATCC	#10259
Aspergillis niger	ATCC	# 9642

At weekly intervals for four weeks, the respective cultures were plated out into Petri dishes to determine the number of microbes present. The results as compared with the baseline number of microbes present when the cultures were first inoculated follow:

	Pseudomonas (Positive Control)	Mixed Bacteria	Mixed Fungi
Baseline (day 1)			
(No Pirfenidone)	52 million (100.0%)	23 million (100.0%)	240,000 (100.0%)
2.0% Broth Solution (Control)			
(With Pirfenidone)			
After 1 week:	<100 (0.0%)	590,000 (2.3%)	<100 (0.0%)
After 2 weeks:	<10 (0.0%)	690,000 (3.0%)	<10 (0.0%)
After 3 weeks:	<10 (0.0%)	1,100,000 (4.4%)	<10 (0.0%)
After 4 weeks:	<10 (0.0%)	510,000 (2.2%)	<10 (0.0%)
5.0% Ointment			
(Pirfenidone)			
After 1 week:	510,000 (0.98%)	57,000 (0.25%)	<100 (0.0%)
After 2 weeks:	1,480,000 (2.8%)	68,000 (0.30%)	<10 (0.0%)
After 3 weeks:	790,000 (1.5%)	65,000 (0.28%)	<100 (0.0%)
After 4 weeks:	180,000 (0.34%)	44,000 (0.19%)	<10 (0.0%)
10.0% Ointment			
(Pirfenidone)			
After 1 week:	260,000 (0.50%)	70,000 (0.30%)	<10 (0.0%)
After 2 weeks:	2,060,000 (3.9%)	166,000 (0.71%)	<10 (0.0%)
After 3 weeks:	1,240,000 (2.2%)	280,000 (1.20%)	<10 (0.0%)
After 4 weeks:	1,020,000	131,000	<10

	(2.0%)	(0.57%)	(0.0%)

(End of Table IV)

The data (Tables I, II, III, and IV) demonstrate that compositions (solutions or ointments) containing pirfenidone at concentrations of 2.0% to 10.0% are distinctly disinfective against aerobic pathogenic bacteria and fungi in a manner typical of antiseptics, and their efficacy increases within a range of increasing concentrations. Disinfectant effects are greatly reduced at concentrations lower than 1.5%.

SAFETY

Primary Skin Irritation Tests:

According to several primary skin (abraded and non-abraded) irritant test in albino rabbits, the primary irritation index is well below 0.5, and therefore the tests samples of the respective compositions cannot be classified as positive skin irritants.

Acute Topical Irritation/Local Toxicity Tests:

(1) Primary Rabbit Acute Eye Irritation Test for 2.0% Pirfenidone Solution

Pirfenidone, as a 2.0% sterile aqueous solution was applied to the eye corneas of six albino rabbits, and failed to cause any irritation as evidenced by the absence of hyperemia, edema, eye discomfort, or chemotaxis (Draize method). The eyes were carefully examined at 1.0 minutes, 30 minutes, and 3 hours after applying the solution, and then repeatedly examined for 10 days after the application of the pirfenidone solution (0.1 ml. per eye).

(2) Primary Rabbit Acute Eye Irritation Test for 10.0% Pirfenidone Modified USP Hydrophilic Ointment

Modified USP hydrophilic ointment containing 10.0% pirfenidone was applied to the right eye corneas of 6 albino rabbits and did not cause any irritation as evidenced by the absence of hyperemia, edema, eye discomfort, or chemotaxis (Draize method). The eyes were carefully examined at 1, 3, 8, 24, and 48 hours and

carefully re-examined daily for 10 days after the application of the ointment (100 milligrams per eye).

(3) Subacute (21 days) Dermal Local and Systemic Toxicity in Albino Rabbits

Graded amounts of modified USP hydrophilic ointment containing 10.0% pirfenidone repeatedly was topically applied to the dorsal aspect of the clipped abraded or non-abraded skin of the back. The graded amounts of ointment were 200 mg/kg/day, 2000 mg/kg/day, and 5000 mg/kg/day. The controls received 5000 mg/kg/day of the placebo vehicle ointment. The rabbits were observed carefully each day for signs of any irritation to the skin (erythema, edema, necrosis, etc.) and were scored according to the method of Draize. They also were observed for any alterations in general appearance and behavior.

No evidence of irritation of the skin (abraded or non-abraded) was seen in any of the groups. No effect was seen at any dose level upon general appearance, behavior, body weight gain, or upon any of the detailed hematological and blood chemistry values, or upon urinalyses. In addition, gross and histopathological examination of several vital organs and tissues failed to show any drug-related changes. In this subacute rabbit experiment, the data indicates that 5000 mg/kg/day of a 10.0% pirfenidone ointment for 21 days is devoid of any demonstrable local or systemic toxicity.

ACUTE ORAL TOXICITY OF 10.0% PIRFENIDONE HYDROPHILIC OINTMENT IN RODENTS

The acute toxicity of the composition cited, determined in female and male rats and/or mice, exceeds 5000 mg/kg/day when administered orally, or topically.

In fasted albino mice, the oral LD50 was calculated to be 11,000 +/- 1,100 mg/kg of body weight. This was determined according to the mortality found over 14 days following administration of the six graded doses to groups of 7 mice per dose level. In fasted

albino rats, the oral LD50 was greater than 10,000 mg/kg body weight, since no deaths and no signs of toxicity occurred.

The following are illustrative examples of the various end use compositions of the invention.

EXAMPLE 1

A modified USP hydrophilic ointment composition was prepared containing, however, 10.0% of pirfenidone. The composition was applied topically to patients who recently experienced lacerations which had become infected. No systemic antimicrobial agents were used. Remission of the infection occurred within 24 hours and complete healing occurred within 5 to 10 days.

EXAMPLE 2

Modified USP hydrophilic ointment composition was prepare containing 10.0% of pirfenidone. The composition was applied topically daily to the toenails of patients with longstanding (several years) fungus infections of the toenails. These infections had been treated repeatedly with many types of antifungal agents without success. The pirfenidone ointment completely cleared these fungus infections in 3 to 12 weeks, and the lesions did not recur on 2-year follow-ups. Pirfenidone is unusual in its ability to penetrate into the collagenous matrix of the toenail, and then into the dermal layers underneath the toenail.

The cited hydrophilic ointment also is very effective in successfully treating, as well as preventing, the fungus infections characteristic of "athlete's foot".

EXAMPLE 3

The composition was prepared and applied topically to patients having a bacterial infection and inflamed local rash at a rate of three times daily. Relief of

discomfort occurred within 1 to 3 hours, and complete healing along with clearing of the rash, was seen after 5 to 7 days.

EXAMPLE 4

The above cited hydrophilic composition was applied to patients having debraded skin due to a scalding burn. Improvement included reduced irritation within one hour and a marked remission was seen in 24 hours after commencement of treatment and subsequently no infections occurred. The composition was applied 3 times daily until full remission was achieved. Complete remission was present after 5 to 7 days.

EXAMPLE 5

In vivo with patients. Intact or ruptured blisters and sharp soreness of "cold sores" (herpes virus #1) on lips and adjacent oral regions of skin were terminated readily after topical daily applications of 10.0% pirfenidone hydrophilic ointment, and the lesions were gone in 5 to 10 days.

In vivo with patients. Various dermal facial warts (papilloma viruses) were eliminated by repeated daily applications of 10.0% pirfenidone hydrophilic ointment, and the warts were gone in 3 to 6 weeks after initiating treatment with the ointment depending on the size of the wart.

EXAMPLE 6

As a barrier ointment or cream, pirfenidone hydrophilic ointment prevents the re-infection of previously treated microbial lesions, and has been repeatedly been observed in patients with various dermal cuts, traumatic injuries, and also in bed-ridden patients with "bed sores".

EXAMPLE 7

An example of a modified USP hydrophilic ointment (10.0% pirfenidone) is as follows:

Pirfenidone (USAN) Powder	100 gms
Propylene Glycol 400 USP	143 ml (143 gms)
Sterile Distilled Water	417 ml (417 gms)
Stearyl Alcohol USP	170 gms
White Petrolatum	170 gms
TOTAL:	1000 gms

EXAMPLE 8

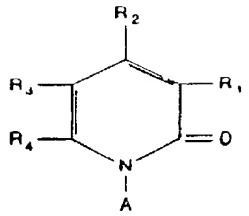
An example of a vanishing cream formula (5.0% pirfenidone) is as follows:

Pirfenidone (USAN) Powder	50 gms
Stearic Acid USP	30 gms
Emplilan SE 40*	30 gms
Isopropyl Myristate	30 gms
Mineral Oil	115 gms
Stearyl Alcohol USP	5 gms
Propylene Glycol 400 USP	50 gms
Sterile Distilled Water	690 ml (690 gms)
TOTAL:	1000 gms

* Trademark

Methods of preparation of pirfenidone and related compounds are described in US Patent No. 3,839,346, issued October 1, 1974, to Gadekar, and titled N-SUBSTITUTED PYRIDONES AND GENERAL METHOD FOR PREPARING PYRIDONES.

In addition to pirfenidone, 2-(1H) pyridone compounds having the following general structural formula have been shown to, or are expected to, have the same antiseptic properties, when applied in the concentrations and vehicles as described above with respect to pirfenidone:



where: R1 = alkyl group (CH3, C2H5, etc.); A is phenyl, thienyl, etc., or other aryl group. The alternate is for R3 to be the site of substitution of the alkyl group with R1 remaining as a hydrogen; R2 and R4 are, in every circumstance, hydrogens.

Examples of the additional 2-(1H) pyridones include:

5-Methyl-1-(3-nitrophenyl-2)-(1H) pyridone
5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone
5-Methyl-1-p-tolyl-2-(1H) pyridone
5-Methyl-1-(3'-trifluoromethylphenyl)-2-(1H) pyridone
1-(4'Chlorophenyl)-5-Methyl-2-(1H) pyridone
5-Methyl-1-(2'-naphthyl)-2-(1H) pyridone
5-Methyl-1-(1'naphthyl)-2-(1H) pyridone
3-Methyl-1-phenyl-2-(1H) pyridone
3-Ethyl-1-phenyl-2-(1H) pyridone
6-Methyl-1-phenyl-2-(1H) pyridone
3,6-Dimethyl-1-phenyl-2-(1H) pyridone
5-Methyl-1-(2'-Thienyl)-2-(1H) pyridone
1-(2'-Furyl)-5-Methyl-2-(1H) pyridone
5-Methyl-1-(5'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(4'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(3'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(2'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(2'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(4'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(2'-thiazolyl)-2-(1H) pyridone
1-(2'-Imidazolyl)-5-Methyl-2-(1H) pyridone
5-Ethyl-1-phenyl-2-(1H) pyridone
1-Phenyl-2-(1H) pyridone
1-(4'-Nitrophenyl)-2-(1H) pyridone
1,3-Diphenyl-2-(1H) pyridone

1-Phenyl-3-(4'-chlorophenyl)-2-(1H) pyridone
1,3-Diphenyl-5-methyl-2-(1H) pyridone
3-(4'-Chlorophenyl)-5-Methyl-1-phenyl-2-(1H) pyridone, and
5-Methyl-3-phenyl-1-(2'-thienyl)-2-(1H) pyridone.

It will thus be seen that the objects set forth above, among those elucidated in, or made apparent from, the preceding description, are efficiently attained and, since certain changes may be made in the above compositions and methods without departing from the scope of the invention, it is intended that all matter contained in the above description.

It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described and all statements of the scope of the invention which, as a matter of language, might be said to fall therebetween.

Claims

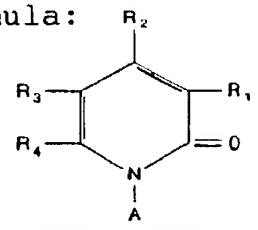
1. An antiseptic topical pharmaceutical substance, comprising: an effective amount of one or more 2-(1H) pyridone compound(s) in a suitable carrier medium.

2. An antiseptic topical pharmaceutical substance, as defined in Claim 1, wherein: said one or more 2-(1H) pyridone compounds(s) is (are) present in an ointment, cream, or foam.

3. An antiseptic topical pharmaceutical substance, as defined in Claim 2, wherein: said one or more 2-(1H) pyridone compounds(s) is (are) present in an aqueous dispersion of one or more substances.

4. An antiseptic topical pharmaceutical substance, as defined in Claim 1, wherein: said one or more 2-(1H) pyridone compounds are present in a concentration of from about two weight percent to about 10 weight percent.

5. An antiseptic topical pharmaceutical substance, as defined in Claim 1, wherein: said one or more 2-(1H) pyridone compounds have the following general structural formula:



where: R1 = alkyl group (CH3, C2H5, etc.); A is phenyl, thienyl, etc., or other aryl group; alternatively, R3 is the site of substitution of said alkyl group with R1 remaining as a hydrogen; and R2 and R4 are, in every circumstance, hydrogens.

6. An antiseptic topical pharmaceutical substance, as defined in Claim 5, wherein: said one or more 2-(1H) pyridone compounds are selected from the group consisting of:

5-Methyl-1-phenyl-2-(1H) pyridone
5-Methyl-1-(3-nitrophenyl-2)-(1H) pyridone
5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone
5-Methyl-1-p-tolyl-2-(1H) pyridone
5-Methyl-1-(3'-trifluoromethylphenyl)-2-(1H) pyridone
1-(4'Chlorophenyl)-5-Methyl-2-(1H) pyridone
5-Methyl-1-(2'-naphthyl)-2-(1H) pyridone
5-Methyl-1-(1'naphthyl)-2-(1H) pyridone
3-Methyl-1-phenyl-2-(1H) pyridone
3-Ethyl-1-phenyl-2-(1H) pyridone
6-Methyl-1-phenyl-2-(1H) pyridone
3,6-Dimethyl-1-phenyl-2-(1H) pyridone
5-Methyl-1-(2'-Thienyl)-2-(1H) pyridone
1-(2'-Furyl)-5-Methyl-2-(1H) pyridone
5-Methyl-1-(5'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(4'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(3'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(2'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(2'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(4'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(2'-thiazolyl)-2-(1H) pyridone
1-(2'-Imidazolyl)-5-Methyl-2-(1H) pyridone
5-Ethyl-1-phenyl-2-(1H) pyridone
1-Phenyl-2-(1H) pyridone
1-(4'-Nitrophenyl)-2-(1H) pyridone
1,3-Diphenyl-2-(1H) pyridone
1-Phenyl-3-(4'-chlorophenyl)-2-(1H) pyridone
1,3-Diphenyl-5-methyl-2-(1H) pyridone
3-(4'-Chlorophenyl)-5-Methyl-1-phenyl-2-(1H) pyridone, and
5-Methyl-3-phenyl-1-(2'-thienyl)-2-(1H) pyridone.

7. An antiseptic topical compound, as defined in Claim 1, wherein: said pharmaceutical substance has the following composition, in weight percent:

Pirfenidone (USAN) Powder	5.0
Propylene Glycol 400 USP	23.5
Sterile Distilled Water	30.5
Stearyl Alcohol USP	20.5
White Petrolatum USP	20.5
TOTAL:	100.0

8. An antiseptic topical compound, as defined in Claim 1, wherein: said pharmaceutical substance has the following composition, in weight percent:

Pirfenidone (USAN) Powder	10.0
Propylene Glycol 400 USP	14.3
Sterile Distilled Water	41.7
Stearyl Alcohol USP	17.0
White Petrolatum USP	17.0
TOTAL:	100.0

9. An antiseptic topical compound, as defined in Claim 1, wherein: said pharmaceutical substance has the following composition, in weight percent:

Pirfenidone (USAN) Powder	50 gms
Stearic Acid USP	30 gms
Emplilan SE 40*	30 gms
Isopropyl Myristate	30 gms
Mineral Oil	115 gms
Stearyl Alcohol USP	5 gms
Propylene Glycol 400 USP	50 gms
Sterile Distilled Water	690 ml (690 gms)
TOTAL:	1000 gms

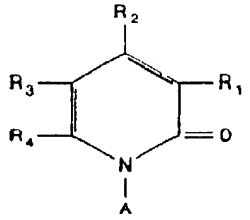
10. A method of treating bacteria, fungi, and/or viruses on the surface of, or within, the layers of the dermis of skin, ears, fingernails, toenails, or hoofs of mammalian species, comprising: applying to said surface or layers a pharmaceutical substance including an effective amount of one or more 2-(1H) pyridone compound(s).

11. A method, as defined in Claim 10, further comprising: providing said one or more 2-(1H) pyridone compound(s) present in an ointment, cream, or foam.

12. A method, as defined in Claim 11, further comprising: providing said one or more 2-(1H) pyridone compound(s) present in an aqueous dispersion of one or more substances.

13. A method, as defined in Claim 10, further comprising: providing said one or more 2-(1H) pyridone compound(s) present in a concentration of from about two weight percent to about 10 weight percent.

14. A method, as defined in Claim 10, wherein: said one or more 2-(1H) pyridone compound(s) have the following general structural formula:



where: R1 = alkyl group (CH3, C2H5, etc.); A is phenyl, thienyl, etc., or other aryl group; alternatively, R3 is the site of substitution of said alkyl group with R1 remaining as a hydrogen; and R2 and R4 are, in every circumstance, hydrogens.

15. A method, as defined in Claim 14, further comprising: providing said one or more 2-(1H) pyridone compound(s) selected from the group consisting of:

5-Methyl-1-phenyl-2-(1H) pyridone
5-Methyl-1-(3-nitrophenyl-2)-(1H) pyridone
5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone
5-Methyl-1-p-tolyl-2-(1H) pyridone
5-Methyl-1-(3'-trifluoromethylphenyl)-2-(1H) pyridone
1-(4'Chlorophenyl)-5-Methyl-2-(1H) pyridone
5-Methyl-1-(2'-naphthyl)-2-(1H) pyridone
5-Methyl-1-(1'naphthyl)-2-(1H) pyridone
3-Methyl-1-phenyl-2-(1H) pyridone
3-Ethyl-1-phenyl-2-(1H) pyridone
6-Methyl-1-phenyl-2-(1H) pyridone
3,6-Dimethyl-1-phenyl-2-(1H) pyridone
5-Methyl-1-(2'-Thienyl)-2-(1H) pyridone
1-(2'-Furyl)-5-Methyl-2-(1H) pyridone
5-Methyl-1-(5'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(4'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(3'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(2'-pyridyl)-2-(1H) pyridone
5-Methyl-1-(2'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(4'-quinolyl)-2-(1H) pyridone
5-Methyl-1-(2'-thiazolyl)-2-(1H) pyridone
1-(2'-Imidazolyl)-5-Methyl-2-(1H) pyridone
5-Ethyl-1-phenyl-2-(1H) pyridone
1-Phenyl-2-(1H) pyridone
1-(4'-Nitrophenyl)-2-(1H) pyridone
1,3-Diphenyl-2-(1H) pyridone
1-Phenyl-3-(4'-chlorophenyl)-2-(1H) pyridone
1,3-Diphenyl-5-methyl-2-(1H) pyridone
3-(4'-Chlorophenyl)-5-Methyl-1-phenyl-2-(1H) pyridone, and
5-Methyl-3-phenyl-1-(2'-thienyl)-2-(1H) pyridone.

16. A method, as defined in Claim 10, further comprising: providing said pharmaceutical substance with the following composition, in weight percent:

Pirfenidone (USAN) Powder	5.0
Propylene Glycol 400 USP	23.5
Sterile Distilled Water	30.5
Stearyl Alcohol USP	20.5
White Petrolatum USP	20.5
TOTAL:	100.0

17. A method, as defined in Claim 10, further comprising: providing said pharmaceutical substance with the following composition, in weight percent:

Pirfenidone (USAN) Powder	10.0
Propylene Glycol 400 USP	14.3
Sterile Distilled Water	41.7
Stearyl Alcohol USP	17.0
White Petrolatum USP	17.0
TOTAL:	100.0

18. A method, as defined in Claim 10, further comprising: providing said pharmaceutical substance with the following composition, in weight percent:

Pirfenidone (USAN) Powder	50 gms
Stearic Acid USP	30 gms
Emplilan SE 40	30 gms
Isopropyl Myristate	30 gms
Mineral Oil	115 gms
Stearyl Alcohol USP	5 gms
Propylene Glycol 400 USP	50 gms
Sterile Distilled Water	690 ml (690 gms)
TOTAL:	1000 gms

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(54) Title: TOPICAL ANTISEPTIC COMPOSITIONS AND METHODS

(57) Abstract

In a preferred embodiment, a method of treating bacteria, fungi, and/or viruses on the surface of, or within, the layers of the dermis of skin, ears, fingernails, toenails, or hoofs of mammalian species, comprising: applying to the surface or layers a pharmaceutical substance including an effective amount of one or more 2–(1H) pyridone compound(s).

Declaration

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1 16 (e)) required)

Attorney Docket Number	183-109(US)
First Named Inventor	Solomon B. Margolin
COMPLETE IF KNOWN	
Application Number	09 / 646,493
Filing Date	March 1, 1999
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

TOPICAL ANTISEPTIC COMPOSITIONS AND METHODS

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) March 1, 1999 as United States Application Number or PCT International Application Number PCT/US99/04412 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1 56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application

I hereby claim foreign priority benefits under 35 U S.C 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

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NAME OF SOLE OR FIRST INVENTOR : [ ] A petition has been filed for this unsigned inventor

1-00

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Given Name (first and middle [if any])	Family Name or Surname
Inventor's Signature	Date

Residence: City	State	Country	Citizenship
Mailing Address			
City	State	ZIP	Country

[ ] Additional inventors are being named on the ____supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.